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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 09/763,370 | 02/21/2001 | Etsuro Ogata | OGATA4 | 9907 |
| 1444 | 7590 | 11/01/2006 | EXAMINER | |
| BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303 | | | HARRIS, ALANA M | |
| | | ART UNIT | PAPER NUMBER | |
| | | 1643 | | |

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/763,370 | OGATA ET AL. | |
| | Examiner | Art Unit | |
| | Alana M. Harris, Ph.D. | 1643 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 17 May 2006.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 2-6,8-15,25-30 and 32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 2-6,8-15,25-30 and 32 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date: _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 17, 2003 has been entered.

2. Claims 2-6, 8-15, 25-30 and 32 are pending.

Claims 6, 8 and 30 have been amended.

Claim 31 has been cancelled.

Claim 32 has been added.

Claims 2-6, 8-15, 25-30 and 32 are examined on the merits.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

3. The rejection of claims 2-6, 8-15 and 25-30 under 35 U.S.C. 112, second paragraph, in sections a, c, f and g as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the amendments to claims 8 and 30.

New Grounds of Objection***Specification***

4. The amendment filed May 17, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the introduction of the term "without" and the subsequent deletion of the term "with" on page 9, line 6. Applicants assert there was an important translational error, Remarks submitted May 17, 2006, page 12, 2nd paragraph. In essence, Applicants assert the Z value in the English translation is incorrectly defined by the formula (measuring value-average for the patients ***with bone metastasis***)/ (standard deviation of a patient without one metastasis) and the Japanese text correctly states the formula including the recitation "***without bone metastasis***". The formula is based on several values that are not provided in the specification. While the specification notes Z values for BALP and osteocalcin on pages 3 and 10 and have values listed in Figure 2, the values used to ascertain these Z values are not provided (i.e. measured values, average for the patients without bone metastasis and the standard deviation of said patients). Moreover, the Examiner cannot read the Japanese language. Consequently, one of ordinary skill in the art cannot verify whether or not the Z value did in fact use an average ***without*** bone metastasis.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

5. Claim 8 is objected to because of the following informality: the term "osteoblastsor" on line 4 of the said claim should be replaced with the phrase "osteoblasts or". Correction is required.

New Grounds of Rejection***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-6, 8-15, 25-30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicants have amended the claims, namely claims 6, 8 and 30 to include the recitation "an average value for patients **without** bone metastasis". As stated in the objection to the specification this translational mistake cannot be verified because one of ordinary skill in the art cannot calculate the Z value due to the lack of values (i.e. measured, average for the patients without metastasis and the standard deviation of a patient without bone metastasis). While Applicants state this amendment is supported by the Japanese text they are

reminded the Examiner is not proficient in the Japanese language. There is not corresponding information provided to support the amendment to the claims.

Applicants' claims, namely independent claims 6, 8 and 30 have been amended to read on methods of diagnosing amelioration and/ or exacerbation of metastasis of malignant tumor to bone in patients with cancer and evaluating the efficacy of drugs for treatment of cancer implementing values (Z values and crossover indexes) obtained from markers for bone formation and bone resorption.

8. The rejection of claims 2-6, 8-15, 25-30 and 32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained and made.

a. Claims 6, 8 and 30 are vague and indefinite in the recitation "and determining a crossover index by dividing said Z value for osteocalcin by said Z value for ..., said crossover index and said ICTP level providing a diagnosis..." .

Applicants assert the characteristic features of the invention and the claims are clear to those skilled in the present art, see Remarks, section b, beginning 15. Applicants inquire as to the Office's questioning of what the number means after the algorithm is completed. Applicants' points of view have been carefully considered, but found unpersuasive.

The question presented in the Final Action mailed November 17, 2005 was whether or not a value obtained by the crossover index was representative

of a particular assessment, i.e. the drugs for treatment were effective or bone metastasis has progressed, for example. If a crossover index yielding a score in the range of 0-5 means cancer has metastasized opposed to a score of 6-10 means the cancer has not. Applicants are requested to clarify how the crossover index score defines or aids in determining whether or not there is amelioration and/or exacerbation of metastasis and the efficacy of drugs for cancer treatment.

b. Claims 2-6, 8-17 and 25-30 continue to be vague and indefinite because it is not clear from the claims how the two markers are used in ascertaining efficacy of a drug and the method steps are not clear.

Applicants argue citing a particular number for the crossover indexes in the claims would render the claims unduly restrictive, see Remarks, page 18, 1st full paragraph. And while this is true the claims should note wherein a result for example, is indicative of metastasis or no metastasis or the drugs administered for cancer treatment were or were not effective. Applicants need not recite a specific number, however the claims should be reflective of the meaning of crossover index. Applicants are requested to ensure clarity and completeness.

c. Claim 8 is vague and indefinite because the claim notes in the preamble that the evaluation of efficacy of drugs is based on assessing one marker of osteoblast activity or one marker of osteoclast marker, see lines 3-5.

Applicants retort the claim is intended to and does recite the use of two markers, one that reflects the activity of osteoblasts and the other reflects the activity of osteoclasts; or a marker that reflects the activity of osteoblasts, see Remarks, paragraph bridging pages 14 and 15.

Applicants seem to note two scenarios: first scenario, is the use of one of two markers, one that reflects the activity of osteoblasts and the other reflects the activity of osteoclasts (see page 5, lines 3-5) and the second scenario, the method steps require three markers, see page 6, lines 4-8. It is not clear what Applicants are attempting to convey. According the preamble the method requires one marker, while the method steps require three markers, see page 6, lines 4-8. The first two markers are bone formation markers (osteoblast markers) and the third is a bone resorption marker (osteoclast marker). Accordingly, the method is still vague and indefinite and Applicants should carefully review the entire claim for consistency.

d. Claim 32 is vague and indefinite because the method steps read on measuring a marker for bone formation and a marker for bone resorption, ICTP, see lines 6-9. However, the conclusion step only cites ICTP values as the determinant useful for assessing progression of cancer metastasis. It is not clear if the bone formation marker listed in lines 6 and 7 of the claim is of consequence in the method determining progression of disease when it seems the said progression is based solely on ICTP. Moreover, it is not clear what variants are being analyzed and what are ICTP values. The claim asserts testing serum for ICTP in lines 8 and 9 of the claim, however that would be considered one assessment opposed to more than one as suggested by the term, *ICTP values*. Applicants are requested to clarify.

e. “[T]he measured values” in line 10 of claim 32 lacks antecedent bases.

f. Claim 32 is vague and indefinite in the recitation "the improvement" in line 6 of the claim. It is not clear what one of ordinary skill in the art is supposed to assess as improved and the recitation lacks antecedent bases.

g. Claim 32 is indefinite in the recitation "expressing the measured values in terms of average of standard error". It is art known to establish a standard error one must have a distribution of several samples or a sample from a population is the standard deviation of the sampling distribution. In the instant case there seems to be only one patient or information gleaned from one sample. Consequently, it is not clear how a standard error is established.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

-Koizumi et al. Bone metabolic markers in bone metastasis of breast cancer. Int. J. Clin. Oncol. 4 : 331-337, 1999; and

-Nakayama et al. Differences in Bone and Vitamin D Metabolism between Primary Hyperparathyroidism and Malignancy-Associated Hypercalcemia. Journal of Clinical Endocrinology and Metabolism 81(2): 607-611, 1996.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The Examiner works a flexible schedule, however she

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can normally be reached between the hours of 7:30 am to 6:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ALANA M. HARRIS, PH.D.

PRIMARY EXAMINER


Alana M. Harris, Ph.D.
30 October 2006